IN THE SPECIFICATION:

On page 14 of the Specification at line 15, please delete the word "casine" and replace it with the correctly spelled word - - casein - -.

REMARKS

The Final Rejection of August 9, 2002 has been reviewed and its contents carefully noted. Reconsideration of this case, as amended, is respectfully requested. Applicants thank the Examiner for his thorough and detailed remarks attached to the Final Rejection and the entrance of Applicant's submission filed on 6/13/02. Claims 6-8, 10, 20, 31-37 and 48 are currently pending. Claims 6-8, 10, 20, 31-37 and 48 are amended herein. No claims are canceled herein. Claims 49 through 76 have been added herein.

New Matter Objection

The Examiner objected to pending claims 6-8, 10, 20, 31-37 and 48 under 35 USC § 112 as containing subject matter which was "described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time of the invention, had possession of the claimed invention" (Final Rejection of August 9, 2002, page 2, last paragraph). It is apparent that the Examiner's objection was to language recited in each of the pending claims with regard to "mammary gland-specific codons" and what the Examiner has termed a lack of "literal support" for such language in the specification. (Final Rejection of August 9, 2002, page 3, first paragraph). To address these concerns, and in compliance with MPEP § 608.04, Applicant has made the amendments required by Examiner to the claims to more plainly reflect the meaning of the specification. It should also be noted, however, that the amendments made to put the claims in better condition for allowance with respect to this point recite language concerning the use of "codon or codons preferred by a mammalian cell for the purposes of expression" (see amended claims 6-8, 10, 20, 31-37 and 48 and new claims 49-76). This new language finds implicit support from the specification generally, and literal support as to its plain meaning at specific locations (see, p. 2 lines 6-11; p. 5, lines 6-14; p. 5 lines 17-27; and p. 6. lines 15-23). More to the point, it goes to the intent of the Applicants to invent a method by which mammalian cell systems generally and transgenic systems specifically could be utilized to

produce proteins or protein fragments that without sequence optimization could not be expressed in detectable or certainly useful quantities. In addition, the Examiner is also respectfully reminded that the Applicants are allowed "to be..[their][sic] own lexicographer," and that if this verbal license leads to any ambiguity the claims are to be construed "in connection with the other parts of the...patent application" as pointed out above. Autogiro Co. of America v. United States, 384 F.2d 391 (Ct. Cl. 1967).

Essentially, according to the claims of the instant invention, the "cell system of choice" and hence the preferred codon profile for optimizing protein expression are the codons preferred by mammalian cells (see, p. 6 lines 13-14; and p. 6 lines 24-25). Given these amendments, and the citations for direct support of them as derived from the specification as filed, Applicant respectfully requests that the objection to the claims on the grounds of "new matter" be withdrawn. MPEP § 2163.06.

Respectfully, should the Examiner maintain his objection Applicants retain their right to appeal or petition this decision to the Board of Patent Appeals and Interference's. Reconsideration and withdrawal of the objection is respectfully requested.

Amendments After Final Rejection

This response to the Examiners Final Rejection includes within it amendments to the claims and the addition of new claims. Amendments such as these can be included within a response to such a Final Rejection if such amendments are made for good and sufficient reasons, as laid out by CFR § 1.116. Justifications for such amendments include: 1) the Applicant's attempt to answer new issues or rejections raised by the Examiner; 2) the amendments reduce the issues to be considered in an appeal; and/or 3) the amendments leave the application in better condition for allowance.

In this instance, and after an in depth review of the Examiner's last response and the guidance provided therein with regard to what the Examiner felt was both enabled by the current invention and the actual "discovery by Applicant" (Final Rejection of August 9, 2002, page 3, second full paragraph, with the quote coming from page 4, second full paragraph) all possible efforts have been put forward to remove all the Examiners' rejections to the remaining claims, and to provide new dependent claims well within the ambit of the invention provided by the Applicants. The Applicant believes that the amendments which have been made, along with the

extensive nature of this response serve to put all the remaining claims in better condition for allowance. This is also true with respect to the canceled claim as well as with the claims which were amended.

Given the above, it is specifically and respectfully requested that the Examiner allow the amendments after final, made herein, and the new dependent claims added.

The Rejection Under 35 U.S.C. §112, first paragraph

Claims 6-8, 10, 20, 31-37 and 48 are rejected under 35 U.S.C. §112, first paragraph for failure to enable a person skilled in the art to perform the invention commensurate with the breadth of the claims. This rejection of the claims, as amended, is respectfully traversed.

The test for claim support under the first paragraph of 35 U.S.C. § 112, is whether the disclosure as originally filed reasonably conveys to the artisan that the inventor had possession at the time of the later claimed subject matter, rather than the presence or absence of literal support. Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 227 U.S.P.Q. 177 (Fed Cir. 1985); In re Kaslow, 707 F.2d 1366, 217 U.S.P.Q. 1089 (Fed Cir. 1983). As has been previously stated by the courts:

> "Enablement is a legal issue. The question is whether the disclosure is sufficient to enable those skilled in the art to practice the claimed invention, hence the specification need not disclose what is well known in the art." *In re Myers*, 410 F.2d 420, 161 USPQ 668 (CCPA 1969); *and see, Lindemann Maschinefabrik GMBH v. American Hoist and Derrick Co.*, 221 U.S.P.Q. 481 (Fed. Cir. 1984).

More to the point, the issue of adequate enablement depends on whether one skilled in the art could reproduce the claimed invention without "undue experimentation." *See,* Wang Labs, Inc. v. Toshiba Corp., 993 F.2d 858, 26 U.S.P.Q.2d 1601 (Fed Cir. 1993); Utter v Hiraga, 845 F.2d 993, 6 U.S.P.Q.2d 1709 (Fed. Cir. 1988). The standard in this inquiry was supplied by the Federal Circuit when that court announced that enablement by a disclosure is not precluded even if some experimentation is required, the only limiting factor is that this experimentation must not be "undue." In re Wands, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). In *Wands* Judge Smith decided that the key word in this formula is "undue" not "experimentation" and

applied a reasonableness standard, given the nature of the invention and the state of the art when he stated:

> "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is **merely routine**, or if the specification in question provides **a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.**" *Wands* at 737 (emphasis added).

Given the above, therefore, it must be understood that when the Applicants, as in the instant specification:

provide a working example in a transgenic system;

detail the benefits and methods of optimizing a given nucleic acid sequence for expression in terms of AT composition in a mammalian transgenic system;

provide a workable means for the removal or replacement of AUUUA mRNA instability motifs,

indicate and then proceed to make specific mutations to overcome mammalian glycosylation issues;

provide extensive guidance to appropriate protocols throughout the specification – including references to old, well-known, and well understood laboratory protocols;

reference many relevant citations in the literature; and

then - **actually produce the exemplary protein in high concentrations in a transgenic animal;** any experimentation that may be necessary, becomes routine.

The practitioner in the field no longer need worry that a certain parasite molecule, like the one derived from *Plasmodium falciparum* and claimed in the instant specification, can be made and expressed in the milk of a transgenic animal, it is known to a certainty that it will. The working example of the current invention produced by the Applicants provides this assurance, and makes irrelevant the difficulties that an inexperienced practitioner may have in referencing the appropriate protocol.

More to the point, many of the characteristics of the MSP-1 protein as well as the DNA and amino acid sequences of *Plasmodium falciparum* as well as other parasites and other parasite proteins are well known by artisans in the field and may be employed in the effort to optimize selected proteins for expression in mammalian transgenic systems. The method of Applicants

and the purpose of the application announces provides a means of making proteins that otherwise cannot be made, or cannot be made in amounts adequate to address and service dire need for critical vaccines around the world.

The protocols disclosed in the specification, provide the public the ability to practice the invention, essentially by providing a detailed map leading towards a goal that has already been reached, regardless of the state of the art prior to the application. In conjunction with the extremely high level of skill in the field, it is clear that the specification, as tempered by the relevant case law discussed above, does enable other workers in the field to make and use the invention without "excessive" experimentation. Wands at 740.

Indeed, the application presents multiple protocols, all well known, that provide for the isolation of the relevant nucleic acid sequences and then provides not only the motivation to optimize them but methods to make sure that decisions taken will also allow the expression system so modified to work in transgenic mammals.

This level of disclosure is **more than** what is necessary for a specification to provide. In determining whether the disclosure requirement is satisfied, the person(s) *skilled* in the art are *presumed* to be aware of all of the relevant literature, including trade publications, textbooks, technical journals, U.S. patents, and old well-known laboratory protocols. Therefore, the Examiners rejection of the claims under 35 U.S.C. § 112, first paragraph, is through the amendments made to the claims and the remarks above traversed, and reconsideration of the claims is, respectfully, requested.

New claims 49 - 76 are dependent upon independent amended claims 6, 7, 10 or 20 as the case may be. As they retain all the elements of the amended base claims from which they depend they should be allowable for this reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 49 - 76 under 35 U.S.C. § 112, first paragraph, in view of the above amendments and remarks.

The Rejection Under 35 U.S.C. §112, second paragraph

Claims 6-8, 10, 20, 31-37 and 48 are rejected under 35 U.S.C. §112, second paragraph for being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. This rejection is respectfully traversed. Each of the rejections enunciated by the

Examiner under 35 U.S.C. §112, second paragraph have been addressed through specific amendment to each of the relevant claims, particularly to remove references to "mammary gland-specific codons". The amendments were made to clarify, particularly point out, and distinctly claim the subject matter of the invention. No claims are cancelled. Reconsideration of the rejection of amended claims 6-8, 10, 20, 31-37 and 48 under 35 U.S.C. § 112, second paragraph, is respectfully requested.

New claims 49 - 76 are dependent upon independent amended claims 6, 7, 10 or 20 as the case may be. As they retain all the elements of the amended base claims from which they depend they should be allowable for this reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 49 - 76 under 35 U.S.C. § 112, second paragraph, in view of the above amendments and remarks.

The Rejection Under 35 U.S.C. §103(a)

Dziegel et al (1993)., *Seed et al.* (1998), *Akashi et al.* (1994), *Bosch et al.* (1994), *and Bleck et al.* (1996),

Claims 6-8, 10, 20, 31-37 and 48 are rejected under 35 U.S.C. §103(a) as being unpatentable over Dziegel et al (1993)., Seed et al. (1998), Akashi et al. (1994), Bosch et al. (1994), in view of Bleck et al. (1996). In response to the Examiner's very thorough comments it should be noted at the outset that all of the existing independent claims have been amended herein to address a variety of the Examiner's concerns as well as to ameliorate some structural and grammatical problems with the claims. Therefore Applicant requests reconsideration of the claims in light of these extensive amendments and claim additions. Given the analysis below, the Examiner's remaining objections to the claims as amended are respectfully traversed.

The Final Rejection of amended claims 6-8, 10, 20, 31-37 and 48 under 35 U.S.C. §103(a) as being unpatentable over Dziegel et al (1993)., Seed et al. (1998), Akashi et al. (1994), Bosch et al. (1994), in view of Bleck et al. (1996), is inappropriate under the United States Supreme Court's guidance enunciated in the three-part test of Graham v. John Deere Company, 383 U.S. 1, 17, 148 U.S.P.Q. 459, 467 (1966). More to the point analysis of the instant claims leads to the conclusion that these claims are not obvious over the prior art reference. *Graham* sets forth, the factual inquiries necessary to determine obviousness. These are as follows:

1. The scope and content of the prior art are to be determined;
2. The differences between the prior art and the claims at issue are to be ascertained; and
3. The level of ordinary skill in the pertinent art is to be resolved.

Graham directs that it is against this background that the obviousness issue is determined.

A. DZIEGIEL *ET AL.* IS NOT AN APPROPRIATE REFERENCE AND DOES DOT FALL WITHIN THE SCOPE OF THE APPLICABLE PRIOR ART.

In the Office Action of April 12, 2000 the Examiner argued that "it would have been obvious to one of ordinary skill in the art at the time of the inventions to modify the nucleotide sequences of Dziegiel ..by decreasing their AT-content and removing mRNA destabilization techniques" (Office Action of April 12, 2000, page 9, third full paragraph). However, this ignores the activities of those skilled in the art at the time of this invention, and is contrary to the level of skill present in the art. The Examiner concedes that Dziegiel does not disclose and is in fact silent with regard to:

the reduction of the AT-content of any selected nucleic acid – including those of *Plasmodium falciparum*;

does not address or demonstrate the removal of any AUUUA instability motifs in any target nucleic acid sequence;

does not contemplate why the removal of AUUUA instability motifs may effect the expression of parasitic protein sequences;

fails to address the alteration of a nucleic acid sequence to increase the use of codons preferred or more abundant in mammalian cells, thereby easing the expression of desired proteins or protein fragments;

does not discuss or provide any guidance with regard to the inclusion of any nucleic acid construct in the cells of host transgenic mammal, and

fails to mention any teaching with regard to the expression or recovery of parasitic proteins in the milk of transgenic animals.

At best, the Dziegiel citation provides is a *Plasmodium falciparum* nucleic acid sequence for use in and with a variety of well known vectors including prokaryotes and viruses. However, it must be noted that in addition to the long list of deficiencies provided above it appears that the Examiner is treating the expression of a given target polypeptide in the milk of a transgenic animal as the expression of a target polypeptide in a vector along the lines of *E. coli,* in essence assuming they are identical in effectiveness and functionality. Respectfully, to do this is to fail to see the true parameters or importance of the instant invention. Applicants wanted to provide a means to reliably produce a protozoan protein that had resisted a multitude of previous scientific efforts at expression, including prokaryote expression. To do this Applicants purposefully employed a secretion system of incredible power and complexity (mammary epithelial cell lactation) that provides for the production and secretion of specific hormonally induced proteins (e.g., milk and milk proteins) in incredibly high concentration and pushes them out of the system of a whole animal in a regular reliable amount, in this way transgenic animals are quite unlike any other tool in the molecular biologists proverbial "tool kit." Dziegiel provides no guidance along this line, and is in fact, completely silent with regard to any differences in various expression systems. Moreover, along with the strength and peculiarities of transgenic mammals as "bio-reactors" the instant invention also provided solutions to a host of expression problems lamented in the prior art, but never overcome by it. Applicants changed the sequence of the target nucleic acid to move towards more "preferred", that is, more available codon sequences in mammalian cell systems while maintaining the overall amino acid sequence of the native protein. Applicants changed the AT composition of the target sequence to again stabilize transcription. Applicants provided for the removal of specific AUUUA instability motifs to improve transcription. Applicants also provided for selective sequence changes to overcome glycosylation problems arising in protein manufacture in transgenic mammals (e.g., N to Q mutations). They then put all of these pieces of the puzzle together and got expression of the target protein in the milk of a transgenic animal. This required a systematic understanding of the host of problems seen before in the prior art and a novel way of using a variety of complex tools to produce the raw material for a needed vaccine. Something which quite simply had not been done before, or reduced to practice. Prior to the elegant solution provided by the Applicants the common practice of those skilled in the art was to attempt production of hard to express parasite proteins without either an understanding of why

they were "hard to express," to provide incomplete or inaccurate guidance (i.e., Dziegiel et al.,), or to attempt modifying expression through the use of only one 'tool' that was in fact only able to overcome one of the problems making expression 'hard'.

The Examiner's analysis thus inappropriately bases its rejection on the use of Dziegiel et al., on the premise that one expression system and all of the interplay in the various tools used to achieve expression of a target protein or protein fragment is like another, and that therefore any cellular expression system with any given target protein is an appropriate and analogous prior art reference for the claimed invention of another such expression system. However, as the Federal Circuit has stated, "[t]wo criteria are relevant in determining whether prior art is analogous: (1) whether the art is from the same field of endeavor, regardless of the problem addressed, and (2) if the art is not within the same field of endeavor, whether it is still reasonably pertinent to a particular problem to be solved," Wang Laboratories, Inc. v. Toshiba Corp. 26 U.S.P.Q. 2d 1767, 1773 (Fed. Cir. 1993); *see also,* In re Clay, 23 U.S.P.Q. 2d 1058, 1060 (Fed. Cir. 1992); (The *Wang* court found that a prior art reference for using a nine bit controller consisting of nine memory chips encapsulated in ceramic dual in-line packages mounted on a circuit board substrate is not in the same field of endeavor as the claimed nine data memory chips for storing digital data on epoxy glass printed circuit board substrate merely because it relates to memories). Id. The Court further let stand a lower Court finding that the prior art reference was not analogous art and was not reasonably pertinent, i.e. the art would not logically have commended itself to an inventor's attention in considering his problem. Wang at 1773, and Clay at 1061. The relevance of the Wang analysis to the instant matter lies in the fact that the Dziegiel reference is not only silent with regard to AUUUA instability motifs, AT – reduction, the alteration of nucleic acid sequences to optimize for mammalian cell expression, and transgenic animals but rather focuses and provides teaching with regard only to simple expression in prokaryote and viral expression vectors – essentially teaching away from the methods required to achieve success in the expression of hard to express parasite sequences. Respectfully, the concerns for expression of protozoan antigen sequences through plasmid vectors, typically in prokaryotes is an entirely different problem, with an entirely different set of concerns and hurdles preventing success than those inherent in the instant invention. (See Dziegiel *et al.*, columns 18-19, and the claims). Thus, though Dziegiel might contemplate the use of similar *Plasmodium falciparum* sequences as those provided in the instant specification, the problem addressed and the solution provided by Dziegiel et al., have little or nothing to do with the

myriad of expression problems overcome by the instant claims, therefore falling outside the scope of appropriate art.

In a similar situation, the Federal Circuit concluded that as between a method and apparatus in which film is transferred to a welding station and a tape splicing machine capable of handling the same film, "[in] the light of all this evidence, one can reasonably conclude that the reference is not within the field of this inventor's endeavor and was not directly pertinent to a particular problem with which the inventor was involved." King Instrument Corp. v. Otari Corp., 226 U.S.P.Q. 402, 405 (Fed. Cir. 1985); *see also,* Union Carbide Corp. v. American Can Co., 220 U.S.P.Q. 584, 588 (Fed. Cir. 1984).

As in the King and Wang situations, the instant claimed invention is directed to features, methods and solutions of problems which are alien and non-analogous to the prior art cited by the Examiner. Therefore the teachings of Dziegiel *et al.*, are not pertinent to the claimed invention.

Accordingly, as in *Wang* and *King,* one must conclude that Dziegiel *et al.* is not within the field of this inventor's endeavor and is not pertinent in any way to the particular problems solved by the invention as provided in claims 6-8, 10, 20, 31-37 and 48. Applicants therefore respectfully request the withdrawal of the Final Rejection of amended claims 6-8, 10, 20, 31-37 and 48 under 35 U.S.C. §103(a) as being unpatentable over Dziegel et al (1993)., Seed et al. (1998), Akashi et al. (1994), Bosch et al. (1994), in view of Bleck et al. (1996) and under 35 U.S.C. §103(a).

New claims 49 - 76 are dependent upon independent amended claims 6, 7, 10 or 20 as the case may be. As they retain all the elements of the amended base claims from which they depend they should be allowable for this reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 49 - 76 under 35 U.S.C. § 103(a), in view of the above amendments and remarks.

B. EVEN IF DZIEGIEL *ET AL.* IS ANALOGOUS ART, DZIEGIEL *ET AL.* TEACHES AWAY FROM THE CLAIMED INVENTION

The present invention claims a multi-faceted system of expressing a parasitic protein, MSP-1, and variants thereof in the milk of transgenic animals – overcoming in the process a host of expression problems experienced with prior methods and protocols that are initiated by the nature of the wild type nucleic acid sequence itself. With regard to the Dziegiel *et al.*, reference the Examiner considers it as a reference that discloses an expression vector system analogous to that claimed in

the instant invention. (Final Rejection of 8/9/02; page 8, second paragraph). As discussed above, the expression system of the current claims focuses on transgenic animals and was developed to overcome not only the problems that transgenic animals have with the expression of a parasite protein but to overcome the structural and sequence problems that mammalian cells may have in expressing certain nucleic acid sequences from protozoans or prokaryotes. This while Dziegiel is **completely silent** to these problems in the prior art and offers only a *Plasmodium falciparum* sequence and broad references to vectors or expression systems that could work. Respectfully, Dziegiel et al., denies any problems with various expression systems and the sequences to be expressed, and teaches that they are interchangeable, which is clearly not the case.

More to the point Dziegiel *et al.*, provides no guidance or teachings to accomplish the sorely needed goal of a malaria vaccine, rather all the citation offers is a antigen sequence – failing to solve the problems of expression in a transgenic or even mammalian system, while keeping the focus on older expression systems (prokaryotes and viruses) that simply were insufficient to produce the parasite protein in sufficient amounts or purity, or in any reliable fashion. Respectfully therefore, the Dziegiel is not only deficient but in fact teaches away from improvements in the delivery of parasite proteins and it is error to find an invention obvious where the prior art reference diverges from and fails to teach or mention the invention at hand. W.L. Gore & Assocs. v. Garlock, Inc., 721 F.2d 1540, 1549-50 (Fed. Cir. 1983). Moreover, as demonstrated by the level of skill in the art as shown by the Dziegiel patent, no one in the industry other than the Applicants has approached the problem of marrying the various requirements for utilizing a transgenic animal expression system for the production of parasite proteins in milk to answer the demonstrated need for a vaccine. The novelty present in the current invention was taking an expression system design to an entirely new level than that performed and suggested by those skilled in the art, to arrive at a transgenic animal expression system proven to produce the needed parasite proteins for the development of a vaccine for a disease which each year kills millions of people. The Applicants' invention is not merely the result of using a variety of molecular biology tools available to many researchers, rather it was the result of recognizing a long term problem, and inventing a solution.

Moreover, the cited reference must disclose to the public an available way of making the product or achieving the result *successfully,* within the constraints of the technically possible and that allowable by law or regulation, if it is to properly remain grounds for a rejection based on obviousness – this Dziegiel et al., does not do. As the United States Supreme Court has stated,

"An inoperable invention or one which fails to achieve its intended result does not negative novelty." United States v. Adams, 383 U.S. 39 at 49-51 (1966). For this reason, failed experiments or inoperative inventions **cannot be considered prior art** sufficient to support an Examiner's rejection, be it one based on anticipation or obviousness. In re Wilder, 429 F.2d 447, 166 U.S.P.Q. 545 at 548 (C.C.P.A. 1970). Here, Dziegiel simply fails to provide any guidance or successful teaching that could lead to the current invention, rather it exemplifies the failures of the prior art. Accordingly, not only is there a difference between the prior art relied upon by the Examiner and the claimed invention, the prior art including Dziegiel *et al.*, such that the cited prior art either teaches away from the current invention or teaches a method or structure for altering an intended and realistic result in the current invention, and in so doing both references are ineligible to support an obviousness rejection. Applicants therefore respectfully request the withdrawal of the Final Rejection of amended claims 6-8, 10, 20, 31-37 and 48 under 35 U.S.C. §103(a) as being unpatentable over Dziegel et al (1993)., Seed et al. (1998), Akashi et al. (1994), Bosch et al. (1994), in view of Bleck et al. (1996) and under 35 U.S.C. §103(a).

New claims 49 - 76 are dependent upon independent amended claims 6, 7, 10 or 20 as the case may be. As they retain all the elements of the amended base claims from which they depend they should be allowable for this reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 49 - 76 under 35 U.S.C. § 103(a), in view of the above amendments and remarks.

C. APPELLANT RECOGNIZES THAT THE LEVEL OF ORDINARY SKILLED IN THE ART IS HIGH

Applicant recognizes that the level of ordinary skill in the art is high. This is supported by the requirement of an understanding of the different abilities, strengths, weaknesses and effects of various protein expression systems, particularly with regard to transgenic animal expression systems. However, in light of the above, even given the relatively high standard of skill in the art, the clear lack of any teaching in any analogous art of applying solutions for the expression of parasite proteins in mammalian cell systems requires a resolution of the *Graham* test with a finding of non-obviousness of the claims. Applicants therefore respectfully request the withdrawal of the Final Rejection of claims 6-8, 10, 20, 31-37 and 48 under 35 U.S.C. §103(a).

New claims 49 - 76 are dependent upon independent amended claims 6, 7, 10 or 20 as the case may be. As they retain all the elements of the amended base claims from which they depend they should be allowable for this reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 49 - 76 under 35 U.S.C. § 103(a), in view of the above amendments and remarks.

II. SECONDARY CONSIDERATIONS INCLUDING LONG FELT NEED

A showing that an invention can satisfy a long felt need for a problem is relevant evidence of the non-obviousness and patentability of an invention. Uniroyal, Inc. v. Rudkin-Wiley Corp., 837 F.2d 1044, 1054-55 (Fed. Cir. 1988). To that end, it is important to note that the Applicants developed a reliable production system for a parasite protein where none existed previously enabling the development of a much needed vaccine.

To demonstrate the ongoing need for a production method of the type presented by the instant invention the Examiner is pointed at two short references present in the current art detailing the continuing need for a reliable parasite protein expression system, and more particularly for a more efficacious malaria vaccine. Graves P., *Vaccines for Preventing Malaria*, COCHRANE DATABASE SYSTM. Rev. 2003; Vol. 1; CD000129 (abstract attached); and, Graves P., *Comparison of the Cost-Effectiveness of Vaccines and Insecticide Impregnation of Mosquito Nets for the Prevention of Malaria*, ANN. TROP. MED. PARASITOL., 1998, Vol. 92(4); 399-410 (abstract attached).

Given the above, Applicant's have demonstrated a long felt and ongoing need in the field for the development of a reliable expression system for hard to express parasite proteins that is the focus of the current claims. This showing provides another indicia of the non-obviousness and patentability of the current claims. Applicants therefore respectfully request the withdrawal of the Final Rejection of amended claims 6-8, 10, 20, 31-37 and 48 under 35 U.S.C. §103(a) as being unpatentable over Dziegel et al (1993)., Seed et al. (1998), Akashi et al. (1994), Bosch et al. (1994), in view of Bleck et al. (1996) and under 35 U.S.C. §103(a).

New claims 49 - 76 are dependent upon independent amended claims 6, 7, 10 or 20 as the case may be. As they retain all the elements of the amended base claims from which they depend they should be allowable for this reason, as well as for the additional recitations they

contain. Applicants therefore respectfully request favorable consideration claims 49 - 76 under 35 U.S.C. § 103(a), in view of the above amendments and remarks.

III. THE EXAMINER FAILS TO MAKE OUT A CASE OF *PRIMA FACIE* OBVIOUSNESS

Establishment of a *prima facie* case of obviousness is a procedural tool for allocating the burden of proof as between an Applicant and the Examiner. The initial burden is upon the Examiner to present this *prima facie* case of obviousness to negative patentability. Respectfully, in the current case the Examiner has failed to establish the needed case of obviousness, thus without more the Applicant is entitled to a grant of the patent. In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992).

A *prima facie* case of obviousness is established when the teachings from the prior art itself suggest the claimed subject matter to a person of ordinary skill in the art. In re Bell, 991 F.2d. 781, 26 U.S.P.Q. 1529 (Fed. Cir. 1993); In re Rijckaert, 28 U.S.P.Q.2d 1955 (Fed. Cir. 1993). The basic considerations which apply to obviousness rejections under MPEP § 2141 are as follows:

(1) the claimed invention must be considered as a whole;
(2) the references must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination;
(3) the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and
(4) reasonable expectation of success is the standard by which obviousness is determined.

When the prior art itself fails to meet even one of the above criteria the cited art does not satisfy 35 U.S.C. § 103(a) and prevents the establishment of the required *prima facie* case of obviousness by the Examiner. In re Oetiker, 977 F.2d 1443, 1445, 24 U.S.P.Q.2d 1443, 1444 (Fed. Cir. 1992); In re Rijckaert, 28 U.S.P.Q.2d 1955, 1956 (Fed. Cir. 1993). As pointed out above, the Dziegiel reference not only fails to render obvious the current claims it also fails to provide any incentive to combine with other prior art.

Moreover, if these failings are insufficient to disqualify the Dziegiel reference it should be noted that if the prior art methodology must be modified in any way to practice the instant invention the prior art citations must also render obvious these modifications or provide a reasonable expectation for the successful practice of the invention with the necessary modifications within the four corners of the references cited be the Examiner. In this case Dziegiel itself, as provided above fails to provide many of the fundamental elements of the current invention provides inaccurate guidance with regard to others, provides no suggestion of any combination with other art and in fact teaches away from the current invention. With these failures, the Dziegiel reference also fails to support any case of *prima facie* obviousness. *In re Oetiker*, at 1446. Thus, the pending claims cannot be obvious over Dziegiel et al. taken alone.

The difficulties associated with developing the instant invention, the long felt need for the invention and the flawed and incomplete methods of the workers in the field is discussed above and all underscore the novelty of the instant invention, but important here is that the combination of citations provided by the Examiner, especially with the flaws of the Dziegiel et al., citation, prevent the establishment of any prima facie case by the Examiner using this citation.

Other Citations

Bosch *et al.* does not provide what Dziegiel et al. lacks. That is, Bosch *et al.,* must present the protocols and methods to overcome the difficulties in expressing parasite proteins in mammalian cell systems generally and transgenic mammals in particular, this is does not do. Bosch et al., must also provide guidance as to how to go about the business of codon optimization of a parasitic protein or protein fragment and/or AUUUA instability motifs in transgenic mammalian systems while ensuring that actual expression would occur, this it fails to do. It must do all of these because Dziegiel fails to even open discussion on these topics, and to render the instant claims obvious these elements of the invention must have been available to the public prior to the instant application. The citation utterly fails to discuss the degree to which codon optimization must be used generally, or in mammals in particular. It also fails to address the alteration of nucleic acid sequences in an effort to move towards codons preferred by mammalian expression systems, upon close review Bosch et al. fails to even suggest these techniques. Instead Bosch et al., provides a primer on *Bacillus thuringiensis* and the production of toxin crystals derived from that species of bacteria (Bosch et al., Column 1, lines 6-15). It should be reiterated that the system of the invention is a

transgenic living mammal, it is highly unlikely that anyone in the field of transgenics would look to a reference promoting the intracellular production and accumulation of toxin crystals in plants for guidance on how to allow or optimize the production of a parasite protein in a whole animal secretory expression system (see Bosch Column 1, lines 5-20; claims). In this light Bosch et al., like Dziegiel et al., is non-analogous art simply incapable of supporting an obviousness rejection of the instant claims, or even making itself available for such a combination. There are simply no teachings to allow the methods of Bosch et al., to make themselves available for an artisan in the field of transgenic mammals. Bosch et al., fails to provide any discussion of any expression system other than prokaryotes and plants and in this way fails to understand or make obvious the true nature of the instant invention – the systematic use of a wide variety of molecular biology tools to overcome a panoply of expression problems for parasite proteins in transgenic mammalian systems. Given this, the Bosch *et al.* reference is simply inapposite to the invention at hand and fails to provide a disclosure capable of sustaining an obviousness rejection of the instant claims alone or in any combination.

Seed et al., does not provide what the other citations lack. As stated previously in response to the Examiners' use of Seed et al., this citation fails to provide any discussion or guidance with regard to a transgenic mammalian system, fails to discuss the methods of improving expression in those systems and fails to discuss or provide any teachings with regard to the expression of parasite proteins in the milk of transgenic mammals. Like Dziegiel et al., discussed above, Seed et al, provides no guidance with regard to the difficulties that can be experienced with protein expression when the sequences of interest have several layers of problems that must be overcome to allow and/or optimize expression in a transgenic system. Moreover, Seed et al., does not attempt to suggest a combination with any other art. Therefore Seed et al., cannot negative or render obvious the instant claims taken alone, and provides no suggestion of combination with any other techniques to come close to the instant invention.

Akashi et al., does not provide what the other citations lack. As previously stated Akashi et al., simply fails to address, and therefore cannot overcome, the problems associated with the expression of parasitic proteins in the milk of transgenic mammals. More to the point, Akashi does not contemplate the removal of one or more AUUUA instability motif codons to improve

the expression of a parasitic protein nucleic acid sequence to enhance the expression of such a desirable exogenous protein. Akashi also simply fails to contemplate the desire to change the AT content of target nucleic acids to enhance protein production in mammalian systems. In fact, Akashi et al., essentially only provides an overview of hematopoietic growth factors and oncogenes. As with the other citations provided by the Examiner, respectfully, Akashi et al., cannot negative the instant claims when taken alone or when provided in the combination assembled by the Examiner. Moreover, this citation provides no suggestion of combination with any other references to render the claims obvious.

Bleck et al., does not provide what the other citations lack. Bleck et al., provides a transgenic mouse expression system that is capable of expressing a protein normally found in the milk of mammals – α lactalbumin. In this case the source of the exogenous milk protein was a bovine nucleic acid. Respectfully, by providing this citation as an example of a transgenic production system the Examiner exemplifies the novelty of the current invention. The bovine lactalbumin sequence of Bleck et al., was native not only in a fellow mammal, but is a protein regulated by lactation itself. In this situation this nucleic acid sequence and corresponding amino acid sequence should be expected to be produced relatively easily in transgenic mammalian cell systems relying on lactation. The reference provides no guidance with regard to non-lactation controlled proteins, provides no suggestion of combination with any other art and is completely silent with regard to the series of problems associated with the production of a parasite protein in a transgenic mammalian system. It does not discuss the use of codon optimization, it does not mention AUUUA destabilization sequences, it fails to suggest any teachings with regard to AT content. In short it provides only a very limited transgenic system, capable of producing mammalian milk proteins. As with the other citations provided by the Examiner, respectfully, Bleck et al., cannot negative the instant claims when taken alone or when provided in the combination assembled by the Examiner. Moreover, this citation provides no suggestion of combination with any other references to render the claims obvious.

In addition it must be respectfully reiterated that each of the citations provided above fail to recognize, expressly or implicitly, any need, possibility or benefit of combining their disparate teachings in such a way that they might then read on the instant claims. Absent some teaching, suggestion, or incentive supporting this combination, a teaching that is simply not present in any

of the citations provided by the Examiner, the references are incapable of supporting a obviousness rejection under § 103(a). Carella v. Starlight Archery, 231 U.S.P.Q. 644 (Fed. Cir. 1986).

Respectfully, the Examiner must provide more than an odd collection of references that recast some elements of known technology, and other elements that may hint at the novelty created by the Applicants in the instant invention. The Examiner must provide references that ***knowingly*** suggest the combination of protocols, tests, or principles, which will lead to the invention to be rendered obvious, and read upon its claims. The Examiner has not provided these references. Rather the Examiner has stated that the instant claims are "as a whole..prima facie obvious" (Final Rejection of August 9, 2002, page 10, last line of the page). Without more, this is a classic reproduction of the invention from improper hindsight, which cannot be used to negative patentability or establish the required case of *prima facie* obviousness. In re Fine, 837 F.2d 1071, 1075, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988).

The important point here is that with regard to the above rejections under 35 U.S.C. §103(a), it should be pointed out that to support the combination of various sources to create an obviousness rejection those sources must themselves specifically contain or objectively suggest to the skilled artisan a combination of art to achieve the invention. To allow anything less would be to render 35 U.S.C. §103(a) a subjective measure of patentability without any parameters or objective standards. This is what the Federal Circuit has squarely decided against in its statements about the improper application of hindsight to sustain an obviousness rejection. This is why the disclosures drawn upon by an Examiner must explicitly contain all the necessary techniques and suggest the combination that would lead to the invention as claimed in a factual and objective way. In re Dillon, 919 F.2d at 696, 16 USPQ2d at 1904 (Fed. Cir. 1990)(*en banc*); In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); In re Geiger, 815 F.2d 686, 2 USPQ2d 1276, 1278 (Fed. Cir. 1987). This the multitude of references cited by the Examiner do not do. Respectfully, the shear number of references cobbled together do much to underscore the novelty of the instant claims.

Respectfully, it is thus the objective measure of obviousness that the prior art cited of record is incapable of supporting, thus preventing the maintenance of a 35 U.S.C. §103(a) rejection. Applicants therefore respectfully request the withdrawal of the Final Rejection of amended claims 6-8, 10, 20, 31-37 and 48 under 35 U.S.C. §103(a) as being unpatentable over

Dziegel et al (1993)., Seed et al. (1998), Akashi et al. (1994), Bosch et al. (1994), in view of Bleck et al. (1996) and under 35 U.S.C. §103(a).

New claims 49 - 76 are dependent upon independent amended claims 6, 7, 10 or 20 as the case may be. As they retain all the elements of the amended base claims from which they depend they should be allowable for this reason, as well as for the additional recitations they contain. Applicants therefore respectfully request favorable consideration claims 49 - 76 under 35 U.S.C. § 103(a), in view of the above amendments and remarks.

Other than a fee for the extension of time no fee is deemed necessary in connection with the filing of this Amendment after Final Rejection. However, the Commissioner is authorized to charge any fee which may now or hereafter be due for this application to GTC Biotherapeutics' Deposit Account No. 502092.

Applicants respectfully submit that the pending claims of this application are in condition for allowance, and that this case is now in condition for allowance of all claims therein. Such action is thus respectfully requested. If the Examiner disagrees, or believes for any other reason that direct contact with Applicant's attorney would advance the prosecution of the case to finality, the Examiner is invited to telephone the undersigned at the number given below.

Early and favorable action is earnestly solicited.

Respectfully Submitted,

Date: 2/10/03

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Claim Appendix

6. (Twice Amended) A method for producing a parasite protein of fragment thereof in the milk of a non-human transgenic mammal, comprising:

providing said non-human transgenic mammal whose genome comprises a modified nucleic acid sequence encoding said parasite protein or fragment thereof operably linked to a promoter which directs expression in a mammary gland, wherein said modified nucleic acid sequence has been modified by replacing one or more AT-containing codons of said modified nucleic acid sequence as it naturally occurs in a parasite with a codon or codons preferred by a mammalian cell for the purposes of expression and encoding the same amino acid as a replaced codon as derived from said parasite; and allowing said non-human transgenic mammal to express said parasite protein or fragment thereof in its milk, to thereby produce said parasite protein or fragment thereof.

7. (Twice Amended) A method for producing a parasite protein or fragment thereof in the milk of a non-human transgenic mammal, comprising:

providing said non-human transgenic mammal whose genome comprises a modified nucleic acid sequence encoding said parasite protein or fragment thereof operably linked to a promoter which directs expression in a mammary gland, wherein said nucleic acid sequence of said parasite protein or fragment thereof has been modified by replacing at least a portion of an AUUUA mRNA instability motif in the coding sequence of said parasite protein or fragment thereof as it naturally occurs in a parasite with a codon or codons preferred by a mammalian cell for the purposes of expression so as to remove said AUUUA mRNA instability motif or prevent said AUUUA mRNA instability motif from destabilizing mRNAs encoding said parasite protein or fragment thereof while encoding the same amino acid as the replaced portion of said AUUUA mRNA instability motif; and

allowing said non-human transgenic mammal to express said parasite protein or fragment thereof in its milk, to thereby produce said parasite protein or fragment thereof, and wherein the naturally occurring nucleic acid sequence encoding said parasite protein or fragment thereof contains at least one AUUUA instability motif.

8. (Twice Amended) The method of claim 6 or claim 7, wherein more than one codon in a naturally occurring nucleic acid has been replaced by more than one codon preferred by a mammalian cell for purposes of expression while encoding the same amino acid sequence as that encoded by said naturally occurring nucleic acid of said parasite protein or fragment thereof.

10. (Twice Amended) A method for producing a parasite protein or fragment thereof in the milk of a non-human transgenic mammal, comprising:

providing a non-human transgenic mammal whose genome comprises a modified nucleic acid sequence encoding said parasite protein or fragment thereof operably linked to a promoter which directs expression in a mammary gland, wherein said modified nucleic acid sequence has been modified by:

a) replacing at least a portion of an AUUUA mRNA instability motif in the coding sequence of said parasite protein or fragment thereof as it naturally occurs in a parasite with a codon or codons preferred by a mammalian cell for the purposes of expression so as to remove said AUUUA mRNA instability motif or prevent said AUUUA mRNA instability motif from destabilizing mRNAs encoding said parasite protein or fragment thereof while encoding the same amino acid as the replaced portion of said AUUUA mRNA instability motif;

b) replacing one or more AT-containing codons of said modified nucleic acid sequence as it naturally occurs in said parasite with a codon or codons preferred by a mammalian cell for the purposes of

expression and encoding the same amino acid as the replaced codon; and

c) allowing said non-human transgenic mammal to express [the] said parasite protein or fragment thereof in its milk, to thereby produce [a] said parasite protein or fragment thereof and wherein the naturally occurring nucleic acid sequence encoding said parasite protein or fragment thereof contains at least one AUUUA instability motif.

20. (Amended) A transgenic non-human mammal whose germline comprises a modified nucleic acid sequence encoding a parasite protein or fragment thereof operably linked to a promoter which directs expression in a mammary gland, wherein said modified nucleic acid sequence has been modified by replacing at least a portion of an AUUUA mRNA instability motif in the coding sequence as it naturally occurs in a parasite with a codon or codons preferred by a mammalian cell for the purposes of expression so as to remove said AUUUA mRNA instability motif or prevent said AUUUA mRNA instability motif from destabilizing mRNAs encoding said parasite protein or fragment thereof while encoding the same amino acid as the replaced portion of said AUUUA mRNA instability motif and by replacing one or more AT-containing codons of the nucleic acid sequence of said parasite protein or fragment thereof as it naturally occurs in the parasite with a codon or codons preferred by a mammalian cell for the purposes of expression and encoding the same amino acid as the replaced codon, wherein said non-human transgenic mammal expresses said parasite protein or fragment thereof in its milk and wherein the naturally occurring nucleic acid sequence encoding said parasite protein or fragment thereof contains at least one AUUUA instability motif.

31. (Twice Amended) The method of claim 10, wherein said modified nucleic acid sequence has at least one codon of the naturally occurring nucleic acid sequence of said parasite replaced with a codon or codons preferred by a mammalian cell for the purposes of expression such that both the AT content of said nucleic acid sequence of said parasite protein or fragment thereof is lowered relative to that of said naturally occurring nucleic

acid sequence of said parasite protein or fragment thereof and the mRNA instability motif of said naturally occurring nucleic acid sequence of said parasite protein or fragment thereof is eliminated by the utilization of an alternative codon or codons preferred by a mammalian cell for the purposes of expression.

32. (Twice Amended) The method of claim 10, wherein each of said AUUUA mRNA instability motifs present in the naturally occurring nucleic acid have been replaced by a codon or codons preferred by a mammalian cell for the purposes of expression so as to remove said AUUUA mRNA instability motif or prevent said AUUUA mRNA instability motif from destabilizing mRNAs encoding said parasite protein or fragment thereof.

33. (Twice Amended) The method of claim 10, wherein said modified nucleic acid sequence further comprises at least one additional codon other than a first codon replaced to lower AT content or a nucleic acid sequence modification made to eliminate said AUUUA mRNA instability motif which has been replaced with a codon or codons preferred by a mammalian cell for the purposes of expression and encoding the same parasite protein or fragment thereof as found in the naturally occurring nucleic acid sequence .

34. (Twice Amended) The method of claim 10, wherein all of the codons of the naturally occurring nucleic acid sequence have been replaced with a codon or codons preferred by a mammalian cell for the purposes of expression and encoding the same parasite protein or fragment thereof as found in the naturally occurring nucleic acid sequence .

35. (Twice Amended) The method of claim 10, wherein said parasite protein or fragment thereof is expressed in the milk of said non-human transgenic mammal at a level of at least 0.5 mg/ml.

36. (Twice Amended) The method of claim 10, wherein said parasite protein or fragment thereof is expressed in the milk of said non-human transgenic mammal at a level which is between 1.0 mg/ml and 2.0 mg/ml.

37. (Twice Amended) The method of claim 10, wherein said parasite protein or fragment thereof as expressed in said non-human transgenic mammal can be detectably expressed in the milk of said transgenic non-human mammal.

48. (Amended) The method of claim 10, wherein all non-preferred codons are replaced with a codon or codons preferred by a mammalian cell for the purposes of expression.

49. (New) The parasite protein or fragment thereof as produced by the method of claim 6.

50. (New) The method of claim 6 wherein said parasite protein or fragment thereof is a protein fragment derived from the parasite Plasmodium falciparum.

51. (New) The method of claim 50 wherein said parasite protein or fragment thereof is a protein, polypeptide or peptide derived from the Plasmodium falciparum protein MSP-1.

52. (New) The method of claim 6 wherein said mammalian cell for the purposes of expression is a mammary epithelial cell.

53. (New) The method of claim 6 wherein said promoter is selected from a group of promoters consisting of:

a) beta-casein;

b) bovine lactoglobulin;

c) whey acid promoter;

d) alpha-ovalbumin; and

e) caprine casein.

54. (New) The method of claim 6 wherein said non-human transgenic mammal is selected from a group of mammals consisting of:

a) caprine;

b) bovine;

c) porcine;

d) rodent; and

e) ovine.

55. (New) The method of claim 6 wherein said modified nucleic acid sequence is modified to provide for the expression of a modified amino acid sequence such that there is at least one Asparagine to Glutamine change to eliminate at least one glycosylation site on said parasite protein or protein fragment thereof produced by said non-human transgenic mammal.

56. (New) The parasite protein or fragment thereof as produced by the method of claim 7.

57. (New) The method of claim 7 wherein said parasite protein or fragment thereof is a protein fragment derived from the parasite Plasmodium falciparum.

58. (New) The method of claim 57 wherein said parasite protein or fragment thereof is a protein, polypeptide or peptide derived from the Plasmodium falciparum protein MSP-1.

59. (New) The method of claim 7 wherein said mammalian cell for the purposes of expression is a mammary epithelial cell.

60. (New) The method of claim 7 wherein said promoter is selected from a group of promoters consisting of:

a) beta-casein;

b) bovine lactoglobulin;

c) whey acid promoter;

d) alpha-ovalbumin; and

e) caprine casein.

61. (New) The method of claim 7 wherein said non-human transgenic mammal is selected from a group of mammals consisting of:

a) caprine;

b) bovine;

c) porcine;

d) rodent; and

e) ovine.

62. (New) The method of claim 7 wherein said modified nucleic acid sequence is modified to provide for the expression of a modified amino acid sequence such that there is at least one Asparagine to Glutamine change to eliminate at least one glycosylation site on said parasite protein or protein fragment thereof produced by said non-human transgenic mammal.

63. (New) The parasite protein or fragment thereof as produced by the method of claim 10.

64. (New) The method of claim 10 wherein said parasite protein or fragment thereof is a protein fragment derived from the parasite Plasmodium falciparum.

65. (New) The method of claim 64 wherein said parasite protein or fragment thereof is a protein, polypeptide or peptide derived from the Plasmodium falciparum protein MSP-1.

66. (New) The method of claim 10 wherein said mammalian cell for the purposes of expression is a mammary epithelial cell.

67. (New) The method of claim 10 wherein said promoter is selected from a group of promoters consisting of:

a) beta-casein;

b) bovine lactoglobulin;

c) whey acid promoter;

d) alpha-ovalbumin; and

e) caprine casein.

68. (New) The method of claim 10 wherein said non-human transgenic mammal is selected from a group of mammals consisting of:

a) caprine;

b) bovine;

c) porcine;

d) rodent; and

e) ovine.

69. (New) The method of claim 10 wherein said modified nucleic acid sequence is modified to provide for the expression of a modified amino acid sequence such that there is at least one Asparagine to Glutamine change to eliminate at least one glycosylation site on said parasite protein or protein fragment thereof produced by said non-human transgenic mammal.

70. (New) The parasite protein or fragment thereof as produced by the method of claim 20.

71. (New) The method of claim 20 wherein said parasite protein or fragment thereof is a protein fragment derived from the parasite Plasmodium falciparum.

72. (New) The method of claim 71 wherein said parasite protein or fragment thereof is a protein, polypeptide or peptide derived from the Plasmodium falciparum protein MSP-1.

73. (New) The method of claim 20 wherein said mammalian cell for the purposes of expression is a mammary epithelial cell.

74. (New) The method of claim 20 wherein said promoter is selected from a group of promoters consisting of:

a) beta-casein;

b) bovine lactoglobulin;

c) whey acid promoter;

d) alpha-ovalbumin; and

e) caprine casein.

75. (New) The method of claim 20 wherein said non-human transgenic mammal is selected from a group of mammals consisting of:

a) caprine;

b) bovine;

c) porcine;

d) rodent; and

e) ovine.

76. (New) The method of claim 20 wherein said modified nucleic acid sequence is modified to provide for the expression of a modified amino acid sequence such that there is at least one Asparagine to Glutamine change to eliminate at least one glycosylation site on said parasite protein or protein fragment thereof produced by said non-human transgenic mammal.